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OPIOID ABSTINENCE REINFORCEMENT DELAYS HEROIN LAPSE DURING BUPRENORPHINE DOSE TAPERING

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A positive reinforcement contingency increased opioid abstinence during outpatient dose tapering (4, 2, then 0 mg/day during Weeks 1 through 3) in non-treatment-seeking heroin-dependent volunteers who had been maintained on buprenorphine (8 mg/day) during an inpatient research protocol. The control group (n = 12) received $4.00 for completing assessments at each thrice-weekly visit during dose tapering; 10 of 12 lapsed to heroin use 1 day after discharge. The abstinence reinforcement group (n = 10) received $30.00 for each consecutive opioid-free urine sample; this significantly delayed heroin lapse (median, 15 days).

DESCRIPTORS: buprenorphine, contingency management, drug abstinence, heroin, positive reinforcement, relapse prevention

Contingency management (CM) has repeatedly demonstrated its ability to help initiate abstinence from opioids or multiple drugs in opioid-dependent individuals during substitution pharmacotherapy (e.g., Jones, Haug, Silverman, Stitzer, & Svikis, 2001; Petry & Martin, 2002; Schottenfeld et al., 2005; Silverman et al., 1996, 2007). Removing or degrading these drug abstinence contingencies typically increases the rate of return to drug use (e.g., Kosten, Poling, & Oliveto, 2003; Preston, Umbricht, & Epstein, 2002).

Despite the ability to initiate abstinence using pharmacological and CM interventions, relapse to drug use remains a challenge. Clients often resume drug use during or shortly after termination of medication dose tapering. Studies have investigated the efficacy of CM for preventing drug relapse in opioid-dependent individuals (Bickel, Amass, Higgins, Badger, & Esch, 1997; Chutuape, Silverman, & Stitzer, 1999; Hall, Bass, Hargreaves, & Loeb, 1979; Hartz et al., 1999; McCaul, Stitzer, Bigelow, & Liebson, 1984). Two studies examined reinforcement of abstinence from opioids (rather than multiple drugs, which is a more difficult goal) during dose tapering from methadone (McCaul et al.) or buprenorphine (Bickel et al.). Each study demonstrated that the experimental treatment was significantly more effective than the control treatment; however, both studies used multicomponent interventions. McCaul et al. used $10.00 and a take-home methadone dose for each opioid-free urine specimen, whereas opioid-positive specimens resulted in forfeiture of these incentives and increased clinic requirements. Bickel et al. used voucher reinforcement of opioid-free urine samples, adherence with therapeutic activities, and community reinforcement. Thus, it is difficult to know whether efficacy of those interventions was due specifically to the opioid-abstinence contingency or to the other components.

The present study aimed to determine whether a single-component, simple positive reinforcement contingency (flat-rate pay for each consecutive opioid-free urine sample) could delay lapse to opioid use relative to a control group that was compensated for attendance and assessment procedures among

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non-treatment-seeking, heroin-dependent volunteers who underwent a 3-week buprenorphine dose taper following short-term maintenance and verified abstinence on an inpatient unit.

METHOD

Volunteers in the control group ($n = 12$) completed an inpatient research protocol involving choices between hydromorphone and money while they were maintained on buprenorphine 8 mg/day for several weeks (Greenwald & Hursh, 2006). Volunteers submitted regular urine specimens and were monitored by research staff throughout their inpatient stay. Once the urine drug test confirmed that the experimental drug from the final session (Friday) had cleared (Monday), participants were discharged from the unit and visited the outpatient program six times weekly (Monday to Saturday) for 3 weeks during a standardized buprenorphine dose-tapering procedure under double-blind conditions. The tapering consisted of 4 mg/day during Week 1 (two small active tablets on Monday to Saturday), 2 mg/day during Week 2 (one small active tablet and one small placebo tablet on Monday to Saturday), and 0 mg/day (two small placebo tablets on Monday to Friday). These volunteers earned $4.00 (paid at each visit by check, which could be cashed nearby) for completing symptom questionnaires (data not reported here) and providing urine specimens regardless of the test outcome.

The experimental group ($n = 10$) was an independent sample that completed a similar inpatient study that also involved choices between hydromorphone and money while they were maintained on buprenorphine 8 mg/day for several weeks (Greenwald & Steinmiller, manuscript under review). Like the control group, they were not discharged from the inpatient unit until the experimental drug cleared from the urine, and they visited the outpatient program on the same schedule and received the identical buprenorphine dose taper. These volunteers differed only in that they could earn a $30.00 payment (paid at each visit by check) for each consecutive opioid-free urine specimen. The first payment was made on the morning of discharge from the inpatient unit, which was designed to ensure that each volunteer sampled the reinforcer (even though there was no opportunity to lapse to drug use prior to discharge). Volunteers were clearly told (first during the informed consent process and then with subsequent reminders prior to discharge) that once their first opioid-positive urine sample was submitted, they would be unable to earn further compensation for opioid-free urine specimens. This contingency was introduced as part of a larger programmatic research plan to increase between-subject variability in time to lapse, so as to examine relations between biobehavioral measures of impulsivity and return to drug use.

Urine specimens were collected and immediately tested on-site during the inpatient stay (prior to discharge) and at each outpatient buprenorphine dose-tapering visit for opioids, methadone, cocaine, and benzodiazepines (all positive cutoff values = 300 ng/ml), barbiturates (cutoff = 200 ng/ml), and cannabinoids (cutoff = 50 ng/ml), using a multitest cup with built-in temperature strip to minimize tampering and thus assure validity of the sample.

The primary outcome measure was time to opioid *lapse* rather than *relapse* for three reasons: (a) Participants were not seeking treatment and were expected to show a minimal delay between return to first use (lapse) and regular use (relapse); (b) a positive urine test might produce a carryover positive result at the next clinic visit, leading to nonindependent observations; and (c) censoring each participant's data at the first opioid-positive sample avoids interpretive problems related to attrition (i.e., nontreatment seekers would be expected to drop out once the opportunity to earn the reinforcer was no longer

available). Furthermore, a flat-rate payment rather than an escalating pay schedule was used for two reasons: (a) It is simpler, and (b) participants might not perceive it worthwhile or feasible to reinitiate abstinence from a lapse during the relatively brief dose-taper period because it would be necessary to reset the reinforcer amount to a smaller value.

Time to lapse was analyzed using the Kaplan-Meier survival curve module within GraphPad Prism Version 4. The unit of analysis was each participant's time (days) until submitting an opioid-positive urine specimen following discharge from the inpatient unit, with a possible range from 1 to 20 days (i.e., the duration of the outpatient buprenorphine dose-taper period). The analysis program automatically converted the entered data for each group into the proportion surviving (remaining abstinent) at each post-discharge day and statistically compared the two curves using a log-rank test (evaluated with a χ^2 distribution and hazard ratio). The one-tailed rejection region was set at $p < .05$.

RESULTS AND DISCUSSION

The control group ($n = 12$) and experimental group ($n = 10$) did not significantly differ (all p values $> .10$) in gender distribution (75% vs. 80% male), percentage of subjects currently injecting heroin as the primary route of use (58% vs. 60%), mean age (45.6 vs. 42.8 years), level of education (12.8 vs. 11.6 years), lifetime duration of regular heroin use (19.6 vs. 19.8 years), or current number of $10.00 bags of heroin used daily (3.9 vs. 3.0).

Figure 1 (top) illustrates that the $30.00 opioid abstinence contingency markedly delayed time to opioid lapse in the experimental group relative to the control group. The survival curves indicate the rate at which these nontreatment-seeking volunteers remained abstinent from heroin over time. Median survival time for the control group was only 1 day, reflecting rapid lapse to heroin the day after inpatient discharge for 10 of 12 participants and on Days 2 and 9 postdischarge for the other 2 participants who received payment only for completing the assessments regardless of urinalysis outcome. By contrast, median survival time for the experimental group was 15 days (range, 1 to 20 days). This apparent group difference in time to lapse was confirmed by a significant log-rank test, $\chi^2(1) = 16.48$, $p < .001$. The hazard ratio was 3.47 (95% confidence interval, 4.45 to 72.10).

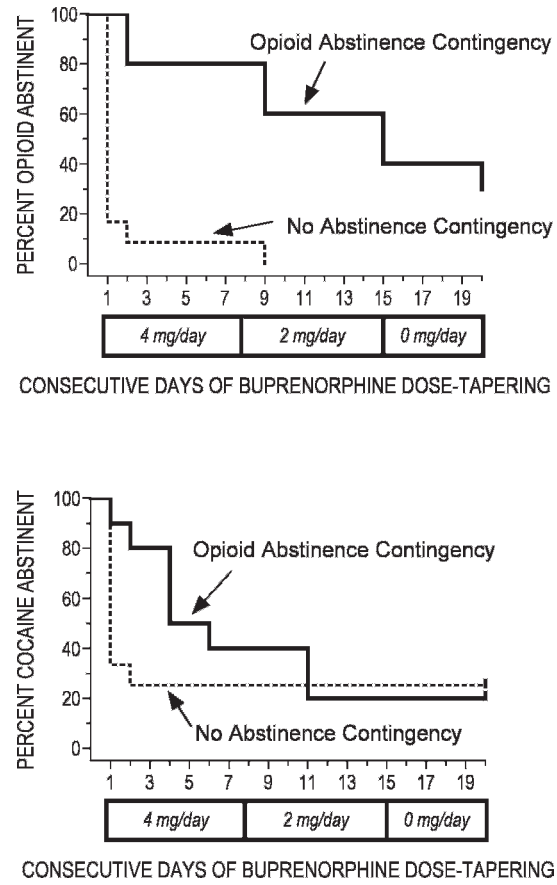

Figure 1. Kaplan-Meier survival curves in the top panel show significantly longer time to opioid lapse in the experimental group ($30.00 payment for each consecutive opioid-negative urine sample) relative to the control group ($4.00 payment for urine samples and questionnaire assessments) during a buprenorphine detoxification protocol. By contrast, the survival curves in the bottom panel show that the opioid abstinence reinforcement contingency did not significantly delay time to cocaine lapse.

Figure 1 (bottom) illustrates that the opioid abstinence contingency did not significantly delay cocaine lapse (median survival, 5 days) relative to the control group (median survival, 1 day), log-rank test, $\chi^2(1) = 0.70$, $p = .40$. Thus, the effect of the experimental contingency was behaviorally specific to opioid use but not to cocaine use.

All participants in both groups, who repeatedly denied during the screening process that they were seeking treatment for their drug abuse and wished to enroll in the research, can be considered treatment resistant at the time they volunteered. These participants also provided detailed economic information about past 30-day income and heroin purchasing and use prior to these studies and reported purchasing heroin about twice daily (averaging about two $10.00 bags at a time), consuming about $40.00 per day of heroin, and that their expenditure on heroin constituted 72% of their total income (Roddy & Greenwald, in press). Given this daily investment of time and resources in procuring and using heroin, it is hardly surprising that the control group promptly lapsed to heroin use once they completed their inpatient experimental participation and brief period of enforced abstinence. What is surprising is that the $30.00 abstinence contingency (administered every other day, given the typical Monday, Wednesday, Friday outpatient visit schedule) could override these individuals' chronic propensity to use heroin at a high daily level. The potency of this single intervention is notable, given that the total weekly opioid abstinence-contingent payment amount ($90.00) was less than half the usual weekly amount expended on heroin ($210.00) by these treatment-resistant individuals. Whether treatment-motivated individuals might be more sensitive to this same contingency, or whether a lower magnitude reinforcer (either flat rate or escalating in value) would produce similar results is a limitation of this study, but could well be a topic of future inquiry. Another limitation of the study is that participants were not assigned randomly to groups. However, the same well-trained research staff worked with all volunteers, and the sociodemographic and drug use characteristics of the two groups did not statistically differ, suggesting that the findings would have been similar had the participants been assigned randomly to the groups.

To the author's knowledge, this study shows for the first time (a) the efficacy of an isolated opioid abstinence positive reinforcement contingency (i.e., no punishment contingencies or other therapeutic interventions) for reducing opioid lapse, and (b) the application of CM to non-treatment-seeking, heroin-dependent individuals during buprenorphine dose reduction. This novel finding parallels previous reports that patients who are undergoing dose tapering from buprenorphine (Bickel et al., 1997) and methadone (Hartz et al., 1999; McCaul et al., 1984) can benefit from CM interventions. These findings are encouraging for demonstrating the potency of CM with a drug-dependent population that is not presently motivated for treatment and thus offer a conservative test; it is predicted that treatment-seeking individuals might be more receptive to this type of intervention. Work is underway to describe individual differences in sensitivity to this reinforcement contingency.

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